

NOTES ON THE PROPHYLAXIS, SYMPTOMS
AND TREATMENT OF TETANUS

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by

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INTRODUCTION.

In ordinary hospital and private practice in this country, the subject of tetanus happily does not bulk largely in the mind of the profession. The outbreak of war has generally drawn attention to this disease. In contradistinction to the vast majority of wounds seen in time of peace, the deep penetrating wounds caused by bullets, shrapnel and pieces of shell, the destruction of tissue far in from the surface, the ricochet of missiles from the soil, the carrying in of pieces of infected clothing and the length of time that often elapses before antiseptic treatment of wounds can be carried out, all tend to provide suitable conditions for the development of the tetanus bacillus and the elaboration of its toxins.

In previous wars tetanus has been more or less prevalent among the wounded, the ratio of cases to the total varying appreciably. It was 0.15 per cent for the English Army in the Crimean War, 0.2 per cent in the American Civil War and 0.35 per cent in the Franco-Prussian War of 1870. In the French Colonial Wars of the latter half of the nineteenth century the deaths due to tetanus are stated to have been from 3 to 5 per cent /

cent of the total mortality. In the Spanish American War the Spaniards suffered severely, while in the Boer War, owing to the freedom from faecal contamination of the soil of the open Veldt, tetanus was practically non-existent.

When the present war started the occurrence of cases of tetanus was foreseen by the medical departments of the armies of the belligerent nations. As early as the 4th August 1914 we find the Serum Institute of Vienna sending a request by cablegram to the Public Health Department of New York for the immediate delivery of 50 litres of tetanus antitoxin for use in the Austro-Hungarian Army. With the British Expeditionary Force in August 1914 600 doses of serum were sent, its use being at first restricted to cases which had already developed the disease or where for some reason or other its onset was deemed likely. The French and German authorities also took early precautions to provide an adequate supply of tetanus antitoxin, there being a totally insufficient quantity on hand at first. After the Battle of the Marne and the fighting in the Aisne Valley, the necessity was seen for inoculating every wounded man with a prophylactic dose of the serum and arrangements were accordingly made for this to be done. An experienced serum worker was stationed at/

at railhead, with orders to give every wounded man a prophylactic injection, and the Surgeons lower down the line were directed to inquire if one had been given and to give one themselves if it had not. Serum was sent to France in increasing quantities - in September, 1914, 12,000 doses; October, 44,000; November, 112000; December 120,000 doses. Instead of being given at railhead, it was now supplied to the Casualty Clearing Stations, the Field Ambulances and even to Regimental Medical Officers.

Owing to the huge armies engaged in fighting under the conditions of trench warfare in a soil, in parts eminently rich in tetanus bacilli, many cases of the disease have occurred, the number being large when compared with the cases seen in time of peace. When, coupled with this incidence of the disease, we consider the large quantities of antitoxin which are used both for the purposes of prophylaxis and treatment, many avenues of inquiry are suggested:

I. PROPHYLAXIS.

Has tetanus antitoxin sustained its reputation as a prophylactic agent? If it has, in what doses should it be used?

Is there anything to indicate the time when the injection/

injection should be given to insure the fullest measure of protection to the wounded man?

How long does the protection conferred by the use of the serum last, and should the dose be repeated at intervals or not?

II. INCUBATION PERIOD.

Has the incubation period been affected in any way by prophylactic doses of tetanus antitoxin?

III. SYMPTOMS.

Has anything been added to the symptomatology of the disease by our experience of it in this war?

Has the use of serum as a prophylactic measure had any effect in altering the picture of the onset of symptoms?

Has the character of the symptoms changed in any way in those cases where full injections of the antitoxin were previously given for purposes of prophylaxis?

IV. TREATMENT.

Has tetanus antitoxin proved efficacious in the treatment of the disease when it has once been established?

In/

In what doses is its use to be commended? How should it be administered? It has been given subcutaneously, intramuscularly, intravenously, intrathecally, and by the intracerebral route. By which of these channels has its use proved most efficient?

Many methods of treatment have from time to time been suggested by various workers and, judging from the cases published, the results in some instances appear to have been surprising. What success has attended the cases treated on these lines?

The relative value of the many therapeutic agents used for alleviating the spasms is also suggested as worthy of consideration.

REPORT ON CASES OF TETANUS.Case 1.

The first case of tetanus that happened to come under my care was when I was a House Physician. I describe the case here because the whole picture of the symptoms and the progress of the disease contrasts so unfavourably with cases I saw later when on service in France. Very full notes of the case were taken at the time, of which the following is a summary:-

Patient - F. F., male, aged 24 years, married, well-nourished, healthy and of a bright, cheerful disposition; by occupation a farm labourer.

History.

On October 2nd, 1909, in the course of his employment he cut his right hand with a hedge bill-hook across the hypothenar eminence, about $1\frac{1}{2}$ inches below the wrist. The wound was a clean incised one, 2 inches long, and deep, but not to the bone. He was taken straight away to his doctor who washed the wound out with 1 in 20 solution of carbolic and stitched it with silkworm gut. He was seen by the doctor on the 2nd, the 5th, the 9th day, when the stitches were removed, and the 12th day after his injury. On the last occasion he was told to return on the next day as the wound was not looking clean. That same afternoon, that/

that is, on the afternoon of the 12th day he complained of pain in the back and shoulders. There was no pain or stiffness of the jaws. On the next morning, the 13th day, he went to his doctor, told him about his back and was given a diaphoretic mixture as he had a slight temperature. That afternoon for the first time he complained of stiffness of his jaws and went to bed at 4.30 p.m. He got steadily worse, the stiffness of the jaws increasing, swallowing and speaking becoming difficult, and perspiration being very profuse. He slept at intervals through the night. His wife noticed that "his mouth was drawn" - the risus sardonius.

The doctor was sent for next day, the 14th day, and he was sent into hospital where he was admitted at 4.45 p.m. on October 16th, 1909.

State on Admission.

He was perspiring profusely, the risus sardonius was well-marked and he had slight twitching of his limbs and facial muscles incessantly. He complained of pain in his back and chest, evinced a great objection to light and swallowed with much difficulty. His head was slightly retracted.

Temperature 98.4° Fah.: pulse 112: respirations 24 per minute.

Progress/

Progress of Case.

He was operated on shortly after admission, the anaesthetic being ether. The wound was opened up and cleaned and the skin round the edges was excised.

Tetanus antitoxin from the Lister Institute, not standardised, was injected, 10 c.cs. intrathecally, 20 c.cs. intravenously and 60 c.cs. subcutaneously in the neighbourhood of and above the wound. He was quiet till 1.45 a.m. Then clonic spasms began, the muscles of the right leg, both arms and the face being chiefly affected. Specially intelligent nurses were put on to give him their undivided attention and to note everything that transpired.

He was given chloral hydrate by the mouth at intervals through the night, 60 grs. in all being given. He slept $3\frac{1}{2}$ hours.

The spasms lasted for about half a minute on the average and numbered 18 during the night.

17th October.

During the day the number of spasms were 13, varying greatly in severity and lasting from a few seconds to 4 minutes.

In the earlier part of the day the muscles of the left arm and left side of the face and neck were most affected, but towards the afternoon the spasms became more/

more generalized and lasted longer, opisthotonos showing itself for the first time in this case.

During the night the patient had 14 spasms, the spasms at first being generalized with marked opisthotonos, then becoming less frequent and less severe, only the left arm and face being affected in the later ones, this reduction in severity and frequency corresponding with increased doses of chloral hydrate.

In all 2 drachms of chloral were given in the 24 hours. Fresh supplies of tetanus antitoxin having been obtained, 100 cc.s in all were injected subcutaneously at intervals during the day in the right forearm above the wound and in the abdomen. The patient perspired very profusely and his general condition was worse.

Temperature 100.4° Fah.: pulse 130 and respirations 38 per minute.

18th October.

The patient seemed better during the forenoon. He had some spasms affecting the left arm and face with slight opisthotonos, but they were of a few seconds duration. At noon he was seized with a sudden severe generalized spasm with marked opisthotonos which lasted for four minutes. His pulse became very rapid. He was given chloral hydrate, 30 grs. and potassium bromide/

bromide 60 grs. per rectum and retained it. Tetanus antitoxin, 80 cc.s, was injected subcutaneously.

During the day he had 19 spasms. Some time after the rectal injection of chloral he became very cyanosed, his extremities were blue and cold and his condition so serious that chloral was discontinued.

At 8 p.m. the temperature was 102.4° Fah.: pulse 150 and respirations 36 per minute.

The patient's condition was now desperate. The spasms were becoming more prolonged and severe and $\frac{1}{2}$ gr. of morphia was given hypodermically. During the night he had 65 spasms, most of them being extremely severe.

He died at 5 a.m., his death being brought about by sudden asphyxiation during a prolonged spasm.

Here we have the picture of a case with a fairly long incubation period, but which had received no prophylactic injection of antitoxin. The antitoxin as issued at that time was not standardized and as much was given him as could be obtained.

Case II./

Case II.

Pte. G. Wounded on June 17th 1916. The wound was a deep flesh one on the outer side of right thigh, a little below the middle line. He had received a prophylactic injection of 750 units which he stated was given him at the advanced dressing station about 3 or 4 hours after he was wounded. On June 30th, while dressing his wound, I noticed that his right leg was twitching and he stated that he had felt twitching two or three times that morning. No notice was taken of it. The next day I was sent for by the nursing sister because the patient complained of stiffness in the jaws and neck.

Antitetanic serum, 5000 units, were injected intrathecally under chloroform and his wound was syringed out with peroxide. Fifteen hundred units of serum were injected subcutaneously in the thigh and abdomen alternately at intervals of four hours, 7500 units being given in this manner during the day and night. The patient perspired slightly but was comfortable and slept fairly well. There was no generalized spasm.

2nd July.

The stiffness in the neck and jaw were still present and the hamstring muscles and the quadriceps extensor were in a state of tonic contraction. He also/

also complained of stiffness in the back. He was given 10000 units subcutaneously.

3rd July.

He could open his mouth more freely and the stiffness of his neck and back were less. There were no twitchings of the limb, but the muscles still felt hard. Seventy-five hundred units were given subcutaneously.

4th July.

His general condition was much the same. His neck and back were still stiff but the muscles of the limb showed less tonic contraction, fibrillary twitchings being noticed in them. He was given 7500 units subcutaneously.

5th July.

The neck and back seemed less stiff but twitching of the limb reappeared. He was given 10000 units, 5000 intramuscularly into the upper part of the thigh and 5000 subcutaneously. An urticarial rash appeared on the shoulders and chest.

7th July.

The stiffness of the back and neck had disappeared. There were still some fibrillary twitching of the muscles of the thigh, but there seemed no difference in the hardness to the feel from the muscles of the other/

other thigh. Subcutaneous injections of 3000 units of serum were given.

10th July.

All symptoms of tetanus had practically disappeared. He was given 3000 units of serum.

He made an uneventful recovery, 1500 units being administered again subcutaneously on the 16th July.

I saw him last on the 19th July when I was moved on to where my work consisted in giving early prophylactic instead of therapeutic injections of antitetanic serum. From a medical officer at the base hospital I heard later that he had been evacuated towards the end of July.

This case has been selected from among four that came under observation for the purpose of contrast with the previous one. Further comment will be made later on in the course of this thesis.

THE PROPHYLACTIC USE OF TETANUS ANTITOXIN.

In 1890 von Behring and Kitasato showed that animals could be immunized against tetanus and that when so immunized, their blood serum when injected, possessed the property of protecting other animals against the tetanus bacillus and its toxins. They thought this was due to a substance in the serum which they called "antitoxin".

From experiments on animals it was proved that:-

1. When a fatal dose of toxin was mixed with a suitable quantity of antitoxin before being injected, it gave rise to no bad effects whatever.
2. If a sufficient amount of antitoxin be injected 24 hours before administering a fatal dose of toxin, the animal was in no way affected.
3. When a suitable dose of serum was injected shortly after a fatal dose of the toxin, the animal did not die and the evil effect of the toxin was considerably inhibited.

These results would lead us to expect that in tetanus antitoxin would be found a valuable prophylactic agent. Such has proved to be the case.

Of all animals the horse is one of the most susceptible to the tetanus toxin. The bacillus appears to/

to be a normal inhabitant of the intestines of cattle and horses. Lukas (1914) isolated the tetanus bacillus from the faeces of 16 out of 17 horses. To veterinary surgeons, tetanus has been a very real danger both because of the great susceptibility of the horse and the liability of wounds being infected by stable refuse. To the practice of veterinary surgeons we are therefore indebted for the early proofs of the value of antitoxic serum as a prophylactic agent.

Vaillard (1912. p.224) states that in the practice of eight veterinary surgeons from 1898 to 1906, 13,124 animals were inoculated after operations or accidental wounds and that not a single case of tetanus occurred among them. During the same time two veterinary surgeons alone saw 139 cases of tetanus among animals that received no treatment.

Dieudonné (1909) recorded 1,009 operations for castration or hernia, with no case of tetanus, while during the same period he saw 87 cases of tetanus among horses operated on or wounded which had not had a prophylactic injection. Vaillard (1912) refers to cases of tetanus seen after wounds received on July 4th (Independence Day) in America. In 1903 there were 415 cases of tetanus. After this prophylactic injections of serum were strongly urged and began to be used.

In/

In 1904 there were 105 cases.

In 1905 " " 104 "

In 1906 " " 89 "

In 1907 " " 73 "

Many writers have confirmed the value of prophylactic serum treatment. In 1907 the editor of the Journal of the American Medical Association summed up the case as follows:

"A fairly careful scrutiny of the American literature for the past five years has not brought to light a single report of the development of tetanus in a person who received a timely prophylactic dose of tetanus antitoxin."

Thus we see that the value of tetanus antitoxin as a prophylactic agent was firmly established prior to the outbreak of this war.

All the experience of our military hospitals since August 1914 tends to confirm this.

Sir David Bruce in an interesting note on the incidence of tetanus among wounded soldiers gives the ratio of cases of tetanus to the number of wounded men from the beginning of the war to the end of 1916, the cases which occurred in home hospitals among the wounded sent over from France being the only ones taken into consideration. He gives a diagram which is/

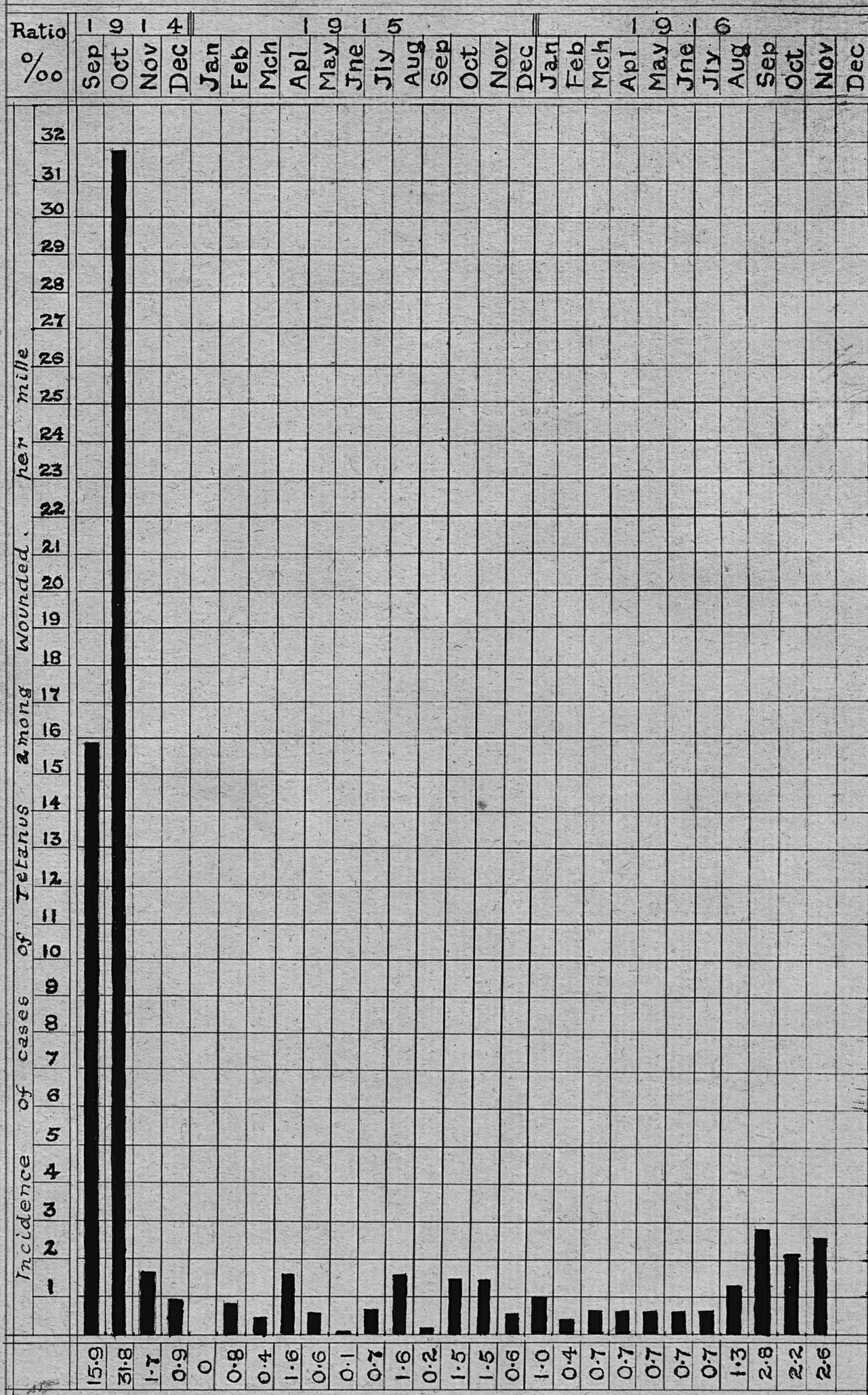


Chart showing ratio of cases of Tetanus to number of wounded soldiers from the beginning of the War to November 1916.

is here reproduced showing that the ratio of cases in September 1914 was 16 per 1000, in October 32 per 1000, while in November 1914 it had fallen to 2 per 1000 at about which rate it remained to the end of 1916.

The prophylactic injection of antitoxin was not carried out in the first two months of the war and it was not until the middle of October that it was adopted as a routine practice in the case of every wounded man. While admitting that the hard fighting with the continual movement of troops, the infective nature of the soil in the Valleys of the Marne and the Aisne and the difficulty of collecting the wounded and giving thorough early surgical treatment might account for the high incidence in the first two months, he believes that the great fall in the incidence of tetanus in November was due to the establishment of the principle of prophylactic injections on a complete scale.

Sir William Leishman also attributed the drop in the incidence to the prophylactic use of the serum and did not think that any large complicating factors came in.

The experience of French Surgeons confirms the value of prophylactic injections of serum. M. Hartmann in a communication to the Académie de Médecine on December 8th, 1914, stated that, among 2473 wounded received/

received at Besancon 36 cases of tetanus occurred with 33 deaths and at Bourg among 900 wounded there were 7 cases of tetanus. No cases occurred at these places in men who had received injections of serum. He believed that if all wounded were given prophylactic injections and if these were repeated 7 days later in anfractuous cases tetanus would disappear.

Bazy in the Comptes rendus de l'Académie des Sciences, vol. 159, stated that in medical units where systematic prophylactic injections were given to all wounded at the moment of entry the incidence of tetanus was 4.18 per 1000. In medical units where the injections were only given to cases thought to be suspicious the incidence was 12.79 per 1000. The incidence was therefore three times greater in those units where injections were only administered to certain categories of wounded than in those where they were systematically given to all wounded.

On account of certain circumstances in a batch of 200 wounded 100 only received a prophylactic injection. Of this series only one man developed tetanus and with him the disease began on the day of injection so that it hardly got a chance to exercise any prophylactic action. In the other batch of 100 which presented wounds comparable to the first batch but received no/
no/

no injection there were 18 cases of tetanus. The incidence was therefore zero in the first batch and 18 per cent in the second.

In Germany also the same benefit has accrued from prophylactic use of serum.

In a communication to the Muenchener medizinische Wochenschrift for December 29th, 1914, Professor Madelung reviewed the collective reports from 80 hospitals in and about Strassburg of the incidence of tetanus from the outbreak of the war. The material collected dealt with 27,677 wounded men. In 37 hospitals where not a single prophylactic injection was given the incidence was 0.77 per cent of the total wounded treated in them. In 39 other hospitals prophylactic injections were given only in selected cases, where from the nature of the wound or the contaminating matter, there was a suspicion of infection by tetanus. In these hospitals the incidence was 0.55 per cent of the total. Even the half measure of using the serum in selected cases made quite an appreciable difference.

In a memorandum on Tetanus by Sir William Leishman issued to medical officers on active service it was stated that there had been in six months only 36 cases of the disease among those who received a preventive dose within 24 hours of being wounded. That this was/

was not due to the possible absence of the cause of infection from the soil was clear from the following facts:

- (1) Bacteriological examination of the wounds had often proved the presence of tetanus bacilli although no tetanic symptoms had followed.
- (2) Many instances of slight trismus or of localised tetanic spasms of a muscle or group of muscles had been reported without the subsequent development of generalised tetanus.
- (3) Thirty-four cases of severe tetanus had been reported during the six months from the very small fraction of wounded men who, for one reason or another had not received a preventive dose of the serum within 24 hours.
- (4) A considerable number of wounded horses continue to develop the disease.

Towards the end of last winter, when the incidence of tetanus among the wounded was very low, in a few weeks 15 cases of tetanus occurred in cases of trench feet which had received no prophylactic dose of serum and steps were at once taken to ensure that every man with trench feet was given a preventive dose.

We thus see that tetanus antitoxin in this war has fully sustained its reputation as a prophylactic agent.

THE FACTOR OF DOSAGE AND TIME OF ADMINISTRATION.

The question of dosage of antitetanic serum involves that of standardisation and of the unit employed. All the serum as used in the British Army is standardised according to the American method introduced by Rosenau and Anderson (1908) and described in Bulletin No.43 of the United States Public Health and Marine Hospital Service, and in the Journal of Hygiene, January, 1914.

The German unit is equal to about 40 U.S.A. units.

Parker Hitchens (1910) proved experimentally that a dose of 300 U.S.A. units of tetanus antitoxin will protect a horse against an infection fatal to the control animals.

Mohler and Eichhorn (1911) found experimentally that as regards an infection fatal to the control -

300 U.S.A. units given 48 hours after infection =
no symptoms of tetanus.

500 U.S.A. units given 72 hours after infection =
no symptoms of tetanus.

700 U.S.A. units given 96 hours after infection =
no symptoms of tetanus.

Whereas -

250 U.S.A. units given 48 hours after infection =
local tetanus. Recovery.

400 U.S.A. units given 96 hours after infection =
local tetanus. Recovery.

They concluded that 500 U.S.A. units was a sufficient dose of antitoxin as a prophylactic, even in cases where the infection had occurred four days prior to the injection of antitoxin.

When we come to consider the dose for a human being we find a statement by Park and Williams (1910) that it was the custom at many dispensaries in New York City and elsewhere to immunize all Fourth of July wounds by injecting 1,000 units and that none of these had ever developed tetanus. From this it would appear that 1000 units is an ample prophylactic dose as it had always prevented tetanus.

The serum as served out to the medical units in the British Army is in ampoules containing 1500 units. The regulations laid down stated that every wounded man was to receive as early as possible a dose of at least 500 units. During the so-called quiet times in the line these injections are sometimes given by the regimental medical officers, sometimes within an hour of the man being wounded. More often the initial prophylactic dose is given not at the regimental aid post, but at the next stage on the line of communications, the advanced dressing station. When an attack is organised special arrangements are generally made. The advanced dressing stations are frequently very much/

much advanced and the task of giving the injections falls to the officers in the main dressing stations of the field ambulances.

When working under high pressure it is not easy to divide the contents of a glass tube into three equal portions, each of which would give a dose of 500 units without allowing for any wastage. The result is that, as often as not, 750 units or half the quantity of an ampoule is used for a dose. By far the great majority receive their injections in well under the 24 hours from the time of their being wounded. The unfortunates, who, owing to various circumstances are not collected or reached by stretcher bearers in time to allow of the dose being given within 24 hours, are comparatively few in number.

Donitz (1897) showed experimentally in rabbits that, if an hour were allowed to elapse between the injection of the toxin and the serum, it required 40 times the neutralizing dose of the serum to save the life of the animal.

MacConkey (1914) in studying the same question on guinea-pigs found that, whereas one-tenth U.S.A. unit of antitoxin neutralized 100 minimal lethal doses (M.L.D.) of tetanus toxin in vitro, it required one unit of antitoxin to neutralize one M.L.D. when given subcutaneously/

subcutaneously and simultaneously but in different parts of the body; and 3 units did not save life when given 4 hours after the toxin. When the serum was given 24 hours after the same amount of toxin, it required 2000 units of antitoxin to save life.

From this it would appear how important it is that as little time as possible should elapse after the wound before the prophylactic dose of serum is given.

To gain information on the value of early prophylactic injection an effort was made to obtain from all the cases reported in our hospitals in France a statement of the exact number of hours that elapsed between the wound and the injection. In 160 cases reported on by Leishman and Smallman this was obtained in 66 cases. In 43 of these cases a preventive dose of 500 or more units was received within 24 hours and among these 62.7 per cent were fatal and 37.2 per cent recovered. In 23 cases in which the time of giving the antitoxin was delayed for more than 24 hours 86.9 per cent were fatal and only 13 per cent recovered. These figures are suggestive even after allowing for the fact that the cases in which the delay occurred were probably late in being collected and therefore more liable to gangrene and to septic trouble.

Another/

Another fact that emerged from their analysis was that in those cases where the dose was delayed, but which recovered, the average size of the dose given was considerably larger than usual, namely, 915 units.

The importance of the early administration of the prophylactic dose was observed by us while at a Base hospital in France. The opening stages of the Battle of the Somme had just been fought and numbers of wounded, both German and British were being brought down the line. The wounds of the Germans were comparable to our own, and they had all received full prophylactic doses of serum, but in the very nature of things, being wounded further afield, in ground strange to our stretcher-bearers, they were probably longer in being collected than the bulk of our own wounded. They therefore received their injections on an average after a longer interval than in the case of our own men. At that particular hospital there were passed through about 8 or 9 times as many British wounded as German. Yet among the British only one case of tetanus developed, while there were three among the Germans. The figures are too small to point a moral from, but it brought home to us at the time the importance of giving the initial prophylactic injection as early as possible.

From/

From the material published there is no evidence that 500 units is not a sufficient dose in all cases, but the general feeling among medical officers in France appears to be that, in severe wounds and especially in those involving comminuted fractures of the larger bones the dose should be increased to 750 or 1000 units; and that the dose should be larger the longer the interval from the time of being wounded.

THE QUESTION OF REPEATING PROPHYLACTIC INJECTIONS.

From experimental evidence it is believed that the immunity conferred by the initial prophylactic dose of serum is largely lost in about ten days. The opinion has become general that the prophylactic dose should be repeated at intervals of about 6 or 7 days in order to anticipate the total disappearance of antitoxin from the body. In a Memorandum, by the Committee on the Study of Tetanus, issued by the War Office, medical officers are enjoined to give second injections after an interval of 7 days to all septic cases; and in long continued, slow-healing wounds, they are advised to practise third, fourth and even fifth injections and so on at regular intervals as long as the cases are suspicious.

The/

The danger of anaphylactic shock when 500 units of antitoxin, contained in 2 or 3 c.cm. of horse serum, are administered is practically negligible whatever the interval between the injections.

Our experience in this war and also the experience of the other belligerents strongly favour the advisability of giving a preventive injection of tetanus antitoxin prior to an operation on a man who has been wounded. Cases have occurred, where a man has been wounded, where his wounds have healed, and some weeks or even months after, for perhaps some reason, such as removing a piece of shrapnel, a small operation has been performed, which has been followed by severe attacks of tetanus directly traceable to the operative interference. It is to be presumed, in these cases, that tetanic spores have remained latent in the neighbourhood of the wound after it healed, and that the injury to the tissues at the time of operation allowed them to germinate. This reminds us of what took place in India in connection with the subcutaneous and intramuscular injections of quinine. In spite of all antiseptic precautions, a number of cases, in which these injections were practised, developed tetanus.

Sir David Semple, Director of the Central Research Institute at Kasauli in a report published by the Government/

Government of India in 1911 explained this:-

"There are people who harbour in their body tetanus spores which may lie dormant in a recently healed up wound or abrasion or possibly in an old healed up injury, long forgotten. There are also many healthy individuals who harbour tetanus in their intestinal tracts. These germinate and develop under certain conditions."

Before operation on any septic wound it is becoming more and more the tendency to give a prophylactic dose of serum, where possible, a day or two before the operation. The tetanus bacillus sometimes establishes itself in blood clots or in the autolysing tissues in the neighbourhood of the wound and with the manipulative interference it is possible that a large amount of toxin may be suddenly set free in the body. The reason for administering the serum some time previous to the operation is that antitoxin injected beneath the skin or into the muscles is said to be absorbed but slowly, taking, it is stated, forty-eight hours in the case of the subcutaneous route and twenty-four by the intramuscular.

THE INCUBATION PERIOD.

When we come to examine the question of the incubation period in the light of the cases that have been reported in this war, we find that in some respects convictions based on former experience have been confirmed. In the cases under review it is quite clear that the shorter the interval between the wound and the attack the poorer chance has the patient had.

Major H. G. Pinches, R.A.M.C. (1915) gives a statement of the incubation period, treatment adopted and results in 39 cases. With -

5	days	incubation	period	there	were	4	cases.	All	died.
6	"	"	"	"	"	3	"	"	"
7	"	"	"	"	"	6	"	1	recovered
8	"	"	"	"	"	8	"	2	"
9	"	"	"	"	"	4	"	1	"
10	"	"	"	"	"	2	"	Both died.	
11	"	"	"	"	"	3	"	2	recovered.
12	"	"	"	"	"	2	"	1	"
15	"	"	"	"	"	1	"	1	"
16	"	"	"	"	"	1	"	1	"
22	"	"	"	"	"	1	"	1	"

From this statement it appears that of 25 cases with/

with an incubation period of 9 days or less, only 4 recovered; while of 10 cases with an incubation period of 10 days or more, 6 recovered.

M. Boguel of Angers in a report to the Académie de Médecine on December 8th, 1914, gave particulars of 31 cases of Tetanus. In -

10	cases	the	incubation	period	was	10	days.	All	died.
18	"	"	"	"	"	8-15	days.	Eight	re-
								covered.	
3	"	"	"	"	"	20	days	All	re-
						or	more.	covered.	

Leishman gives two series of cases with the incubation period and the mortality. In the first series of 69 cases, of 43 fatal cases the average incubation period was 8.83 days, and of 26 cases which recovered the average was 11.57 days, the difference being 2.74 days, smaller than might have been expected. In the second series of 157 cases - of the fatal cases, 115 in number, the average period was 10.7 days, and of the 42 recoveries it was 14 days. Here there is a difference of 3.3 days which corresponds closely with that in the first series.

In all the cases published by Bruce in England and Leishman from France the shortest incubation period mentioned/

mentioned is 2 days and this is reported in two instances, but in one of these it is stated that there was some element of doubt as to the exact day of wounding, the other being a slight case which recovered, where the presumed source of infection was a small cut on the index finger. There are three cases reported with an incubation period of 3 days and thereafter the numbers rise rapidly till the greatest number is reached in France on the 8th day and in England on the 11th day. This was to be expected, as the men with the most severe and most septic wounds are kept in France and a larger proportion of the early and acute cases fall to the lot of the medical officers there.

The longest incubation period recorded, is that by Bruce in his last series, of 365 days. He also records another one of 330 days and we find 32 cases noted with incubation periods varying between 50 and 153 days. From the 50th day downwards the cases increase in number.

This subject of delayed tetanus is an interesting one. It supports Semple's view that spores remain undestroyed in the tissues till they are in some way stimulated to germination. In the cases of delayed tetanus which have lately been reported from time to time it would appear that the onset of the symptoms has/

has generally followed operative interference with the site of an old wound. This emphasises the importance of giving a prophylactic injection before an operation, however small, on a man who has once been wounded.

In these cases with a longer incubation period than 21 days, which may be assumed to be the limit of the normal period, the recovery rate compares favourably with that of the total number of cases.

Sir David Bruce when comparing the curve of the incubation period of the year 1914-15 with that of the year 1915-16 notes that more cases with a short incubation period occurred in the former year and that more cases with a long incubation period occurred in the latter year. In 1914-15 there were 87 cases with an incubation period up to 10 days while in 1915-16 there were only 27 cases with this short incubation period.

In 1914-15 there were only 12 cases with an incubation period of more than 22 days; whereas in 1915-16 the number of such cases was 62.

He states that this difference may be due to the introduction of prophylactic injections which were only begun some months after the beginning of the war on anything like a complete scale.

In his last series of cases Bruce compares the average/

average incubation period of those which received a prophylactic injection on the day of the wound with that of those who received no injection at all. The difference is very marked, the average incubation period of the latter being 15.7 days or just over half the average of those inoculated on the day of wound.

Kummell in the Berlin Klin. Woch., states that in Germany the experience has also been that the picture of tetanus as seen at the beginning of the war has changed and that the incubation period has become longer and the severity of the disease greatly lessened. He attributes the change to the prophylactic use of antitoxin.

SYMPTOMS.

In a disease like tetanus, where, in treatment, you mainly rely on the use of an antitoxic and not a bactericidal serum, it is all important that the diagnosis of the condition should be made as early as possible. When the symptoms of tetanus are distinct, it means that the disease has made considerable headway and the conditions for the use of antitoxin are not so favourable. The chances of recovery diminish rapidly, the greater the length of time after the first symptoms are observed.

Tetanus in its early stages has been mistaken for 'colds', muscular rheumatism, sore throat, mumps, stiff-neck, influenza, commencing pleurisy, etc. In the first case which is recorded earlier in this thesis, the doctor, who sent the case in, told me that at first he thought the man had got a 'touch of influenza.' The man went to him complaining of a feeling of chilliness and pain in his back and shoulders. It will be remembered he was given a diaphoretic mixture as he had a slight temperature.

Where there has been a history of a wound some time previously and there is therefore a possibility of the development of tetanus it becomes of the most urgent/

urgent importance to look out for any premonitory symptoms that may indicate the imminent onset of the classical symptoms of the disease.

K. Evler (1910) gives 13 cases of tetanus with 2 deaths that came under his personal observation, he himself being one of them. He infected himself during an operation and early symptoms developed within 24 hours. He goes into the question of premonitory symptoms and describes them as being very varied and changeable. A memorandum, by the War Office Committee on the Study of Tetanus, for the use of Medical Officers in the army urges the importance of early diagnosis and gives a list of premonitory symptoms.

In 24 hours or so after infection there may be a general restlessness, changing suddenly to a desire to rest.

The face assumes an anxious look.

Pain is complained of in the back and shoulders and sometimes the neck.

There are unreasonable outbursts of temper.

The patient begins to suffer from insomnia with distressing dreams and sometimes nightly delirium.

A sore throat is often one of the earliest features and epistaxis may occur.

Violent headaches and attacks of giddiness are/

are complained of in some cases and excessive yawning often occurs. The vertigo is, in some instances, very marked.

There may be a difficulty of swallowing without a recognizable cause.

There is at times stiffness of the muscles of the neck.

The patient may have a feeling of chilliness and there may be swelling without any apparent local inflammation of the injured part, and throbbing of the arteries of the limb even when it is raised. Evler attributes particular importance to this symptom.

In some cases the first complaint is that of spasm or stiffness in the injured limb.

Slight jerking may follow pressure on the flexor tendons and these muscles may be noticed to be in a state of increased irritability. This has been noticed to occur in horses quite early in an attack of tetanus.

The patient may complain of a stitch in the side or of a feeling of oppression in the chest.

There may be difficulty of micturition due to spasm of the sphincter of the bladder and this may last from a few minutes to as long as half an hour.

The tongue sometimes shows tremor and may be/

be put out to one side.

One of the most frequent early symptoms is a profuse local or general sweating.

When symptoms like these are present Evler believes that an injection of serum should be given as the onset of tetanus is extremely probable. Other symptoms may appear later:

An increased flow of saliva.

Reflex spasms of the oesophagus.

Symptoms connected with the ocular muscles - nystagmus, ptosis and strabismus.

Ear trouble and spasmodic cough.

There may be tremors and spasmodic contractions which are not painful and may not attract attention.

Pain persisting after muscular contraction induced by effort.

Swollen and reddened lymphatics, enlarged glands and tenderness in the infected region.

An effort is being made by the War Office Committee on Tetanus to obtain information on the subject of premonitory symptoms from the medical officers who have had an opportunity of observing them in cases under their care. They attach great importance to these/

these symptoms from the point of view of early diagnosis and treatment.

With the extensive use of prophylactic injections of antitoxin not only has the incidence of the disease been greatly reduced, but the picture of the onset of symptoms has been radically altered and the diagnosis in some instances has become correspondingly difficult. The classical symptoms of the disease as described in text-books refer to a stage when the disease has already made great headway. In patients who have been protected by antitoxin, the incubation period is longer and trismus and generalized spasms in many of the cases do not occur. The first indication of the disease is very often an increased reflex excitability of the muscles around the wound. There are twitchings and rigidity of these muscles and a local increased reflex response to gentle tapping or pressure. This is generally noticed by the person dressing the wound. Theoretically it is easily explained. Tetanus toxin is manufactured by the bacilli in the neighbourhood of the wound, is absorbed by the nerve endings in the muscles and reaches the motor nerve cells by travelling along the nerves and probably by the axis cylinders. In a large number of cases the toxin appears to reach the spinal cord primarily by the nerves which are in connexion/

connexion with the seat of injury and hence the motor nerve cells governing the muscles round about the wound will be the earliest affected and the affection shows itself in the form of spasticity and increased reflex excitability of those muscles. In some cases these symptoms may precede other symptoms of tetanus by many hours. In the second case recorded earlier in this thesis, the twitching and spasticity of the muscles were noticed over 24 hours before any other symptom appeared. My attention was drawn to them while dressing the man's wounds one forenoon. It was on the afternoon of the next day that stiffness of the jaw and neck was noticed and I first became aware that I had a case of tetanus to deal with. Where there is no protection by antitoxin the disease shows no local manifestations of increased irritability or spasticity, but bursts out as generalized tetanus and runs its fatal course in two or three days. Where there is protection by antitoxin the manifestations of tetanus are often confined to local spastic rigidity of the wounded limb which may persist for weeks without becoming generalized.

At the same time as I had the case above referred to under my care, I had an opportunity of observing three cases of tetanus among some wounded Germans.

Two/

Two of them had been severely wounded, one with a compound fracture of the femur, the other with a large shell wound of the buttock. The third was suffering from perforating wounds of the ankle and calf of the leg. Owing to delay in being collected these men did not get their prophylactic injections till some considerable time had elapsed. All three developed severe attacks of tetanus. The incubation periods were short, 6 to 9 days, there were no local manifestations noted, generalized spasms began early and in spite of large doses of serum given therapeutically, they all terminated fatally, death being hastened in two of them by gas gangrene. Evler states that the feature of the early symptoms is that they appear transiently, are slight at first and, as such, are very apt to be missed. It is possible that there may have been premonitory symptoms and local phenomena in these cases, but if there were, they were of very short duration and certainly passed unnoticed. Being particularly interested in tetanus I was keenly desirous of observing the earliest manifestations of any cases that might occur. The hospital staff was however very hard worked at that time as it was in the early days of the battle of the Somme and literally hundreds of casualties were coming in every day. The operating theatres/

theatres were going practically all day and night and we could only get to our wards for short periods at long intervals. Facial spasms in one case and trismus and stiffness of the neck muscles in the two others were what first attracted attention, general spasms following soon after.

In many cases which have received prophylactic injections within a short time of injury it has been found that not only is the incubation period lengthened but the progress and development of the symptoms is slow. The premonitory symptoms in these cases are not so apt to be overlooked and valuable time is gained. The rate of onset is sometimes extended over a period of days and even weeks, and successful treatment is still possible after definite signs of tetanus have existed for several days. At the same time the early diagnosis of such cases becomes more difficult owing to the insidious character of the onset and the apparently trivial nature of the early symptoms.

Major H. R. Dean, R.A.M.C. (1917) discusses the signs and symptoms in a valuable report on 25 cases of tetanus observed during the first four months of this year at the 2nd Western General Hospital. He classifies the cases in three groups:

1. Four cases in which the spasm remained localised to the muscles in the neighbourhood of the wound.

2./

2. Ten cases in which the spasms commenced in the neighbourhood of the wound and remained for a time localised. After a variable interval generalization occurred.
3. Eleven cases in which there was no history of preliminary local spasms, and the disease commenced suddenly by involvement of the jaw and neck muscles.

Referring to the earliest localised symptoms, in some cases the first manifestations were a twitching or slow irregular clonic contractions of the muscles in the immediate vicinity of the wound. In other cases the earliest observed sign was a tonic contraction of a group of muscles, usually a flexor group, near the wound. There was stiffness and pain in one or more of the limbs and some of the cases were at first diagnosed as muscular rheumatism and were treated with salicylates. The conditions sometimes remained localised for days and weeks, and, even in the absence of serum treatment, little change was seen in the symptoms from day to day. There was generally, however, a gradual spread to adjacent groups of muscles.

Generalization of the signs followed sooner or later in the majority of cases, groups of muscles far from the site of the wound becoming affected. The masseters, /

masseters, the posterior cervical muscles, the muscles of the anterior abdominal wall, the spinal muscles in the dorsal and lumbar regions, and the flexors of the hip, knee and ankle joints were most frequently involved. In 3 cases there was spasm of the facial muscles. The muscles of the upper extremities escaped in all the cases except where there was a wound of the hand and arm. Stiffness of the posterior cervical muscles was an early sign of generalization and from there the stiffness spread down to the dorsal region. Extreme rigidity of the abdominal muscles was often a marked feature.

The reflexes of the lower extremities were generally exaggerated. The knee jerk was very violent and was followed by clonic spasms of the quadriceps extensor. Plantar stimulation resulted in an exaggerated response involving all the muscles of the leg and thigh and in some cases there was a crossed response with contractions of the muscles of the other limb.

Ankle clonus was obtained in some cases. In some cases where there was tonic contraction of the hamstring muscles the knee jerk could not be elicited. In other cases there was first a sharp contraction of the quadriceps extensor which was cut short and was followed by a violent spasm of the hamstring muscles,
a/

a kind of double jerk.

Other than in the cases in which the wound was situated in the arm or hand, the triceps jerk was elicited in only two instances.

Profuse perspiration and a quickening of the pulse rate were associated with generalization of the disease. Within 48 hours of a sufficient dose of the antitoxin given intravenously the pulse rate generally fell and Major Dean thinks this a sign worthy of note as an indication as to whether serum treatment is likely or not to prove successful.

ABNORMAL FORMS OF TETANUS

We have seen that the prophylactic use of tetanus antitoxin has in many cases completely changed the aspect of the disease. Purely localized forms have occurred, difficult to recognize as cases of tetanus, and it is possible that many have been missed.

M. M. Courtois Suffit and Giroux (1916) have divided these abnormal or atypical forms of tetanus into three main classes: cephalic, monoplegic and paraplegic.

CEPHALIC/

CEPHALIC TETANUS.

In the cases classed under this heading the source of infection is usually a wound on the head or face. The wound is often so slight and heals so quickly that the clinical signs, when they do manifest themselves, may not at first be connected with it.

This class is subdivided into four subclasses:-

- (a) Non-paralytic cephalic tetanus. This form is the simplest manifestation and is rarely seen. The clinical signs are trismus and contractions of the facial muscles, with or without dysphagia. If the last symptom is present there is pharyngeal spasm and the patient is difficult to feed. Later on the convulsions may spread to the muscles of the neck and there may be respiratory embarrassment. The prognosis on the whole is good and the outlook is brighter if the breathing is not much interfered with.

A hydrophobic form is sometimes seen, closely resembling rabies, in which there are violent convulsive spasms which begin in the muscles near the wound and spread to the adjacent muscles of the face, neck and pharynx, ultimately involving the respiratory muscles and causing intense dyspnoea. These cases are invariably fatal.

(b)/

- (b) Cephalic tetanus with facial paralysis. Most of the cases are of this type. The infection is localised to the area of the trigeminal nerve. The spasms are at first limited to the face and head though they may spread later to adjacent muscles.

Preceding, accompanying or succeeding the spasms there is facial paralysis which may be unilateral or bilateral according as the wound is to one side or the middle line.

If the facial paralysis is total there is hyperacusis and disturbance of the sense of taste; if partial only the superior or inferior branches of the nerve are affected.

This form of the disease may be acute, subacute or chronic. The more chronic the case, the better is the prognosis. The case mortality is about 50 per cent.

- (c) Cephalic tetanus with oculomotor paralysis. This is a rare condition and only occurs when the wound is in the neighbourhood of an eye.

The paralysis is the first and may be the only symptom. The third nerve is always affected. In many cases there is paralysis of the fourth and sixth as well, more or less complete, /

complete, and resulting in ptosis and strabismus.

This form may exist alone or be combined with facial paralysis.

The prognosis is generally a favourable one, especially in the more chronic cases.

- (d) Cephalic tetanus with the hypoglossal nerve affected. Here we have the picture of a labio-glosso-pharyngeal paralysis. This type is exceptional.

MONOPLEGIC FORM.

In cases of this class the clinical signs are localised to a limb, generally the wounded one. The onset may be early or late, varying from 5 days to 3 weeks. In many cases the incubation period may be much longer.

The first indication may be that the patient complains of pain at the site of the wound and, on examination, spasticity or twitchings of the muscles may be noticed. Localised spasms generally follow. The temperature is very little, if at all, above the normal and the pulse is only slightly increased in frequency - from 100 to 120 per minute.

The/

The muscles and nerves show hyperexcitability to galvanic and faradic stimulation.

PARAPLEGIC TETANUS.

This form of tetanus is rare and the cases that have occurred may be classified as belonging to one of two types:

- (a) A superior form in which the arms, forearms and hands are in a position of forced flexion.
 - (b) An inferior form in which the lower limbs are in the position of forced and fixed extension as a whole and the foot in that of equinovarus.
-

TREATMENT OF TETANUS.

A generation has passed away since Professor Kanthack used to impress upon his pupils that cases of tetanus may fall to be classed in one of three groups:-

- (1) Those with a short incubation period which invariably proved fatal and were hopeless from the start.
- (2) Those long in incubating which invariably recovered, no matter what line of treatment was adopted.
- (3) A class of cases, comparatively few in number, and with an incubation period intermediate in length between the other two groups, on which alone the value of any line of treatment could be demonstrated and where the chances, for and against the patient, were so evenly balanced that the scale might possibly be turned in his favour by proper treatment.

Though the prophylactic use of tetanus antitoxin has in all probability modified the relative proportion of the size of these groups by reducing the numbers of the first and increasing those of the second group, yet/

yet on the whole this classification still appears to hold good.

Since the outbreak of this war papers have been published from time to time dealing with numbers of cases that had occurred and giving the results of treatment, in some instances with exhaustive analyses of the figures applicable to the various lines adopted. Tetanus is peculiarly difficult to deal with from this standpoint. The difficulties of estimating the value of the different methods of treatment are much enhanced by the capricious variations in the disease. The incubation periods may be long or short, the temperature and the pulse may from the outset be normal or alarmingly altered and the virulence of the disease may be much affected by the locality in which it occurred. The arguments of the statistician are therefore apt to be unusually misleading in this disease. On the other hand the experience of the clinician in severe cases, carefully observed and recorded should be extremely valuable. It is unfortunate that many of the cases of tetanus in this war occur at times of great stress. With numbers of wounded to attend to, employed in the operating theatres, as they are, for long stretches at a time, many medical officers are deprived of making/-

making use of great opportunities of closely observing interesting cases of the disease.

THERAPEUTIC USE OF TETANUS ANTITOXIN.

In antitetanic serum we have, beyond a shadow of doubt, a perfect antidote for neutralizing the toxin of tetanus. The poison is completely destroyed and rendered inert when brought into contact with the antitoxin. The problem to be solved is how to bring about this contact in the body in the shortest possible time and under the most favourable conditions for neutralization to take place. We may attempt to do this along three lines. The attack may be made on the local factory of the toxin, on the route by which the toxin travels to the central nervous system or on the central nervous system itself. The first method would be the ideal one, but in practice it is found that it is often difficult to locate the focus and that manipulative interference is liable to result in a sudden absorption of large quantities of the poison with the development of a rapid and fulminating attack of the disease. The latter two lines of attack have proved to be more practicable.

When the diagnosis, however early is made and we know/

know that we are dealing with a case of tetanus, the very symptoms which established the diagnosis are in themselves evidence that the toxin has reached the central nervous system and that considerable damage has been done. In the curative use of tetanus antitoxin we hope not only to destroy the free toxin that is present in the blood and tissues and to maintain a sufficient concentration of antitoxin in the blood and lymph in order to destroy all the subsequent output of toxin from the infected focus, but we hope to secure such a concentration in the central nervous system that the toxin which has already reached the nerve cells will be dissociated from them and that any fresh toxin will be neutralized immediately it arrives and before damage to the cells occurs.

It is a debated point whether any toxin that is once fixed can be dissociated. The experimental work of Kraus and Amiradzibi (1910) suggested that a toxin must pass out of a poisoned cell before it can be neutralised by its antitoxin as the latter could not penetrate into the cell, and that the rate of diffusion of the toxin out of the cell is accelerated by the presence of antitoxin in the surrounding fluid. Moreover, von Graff and Menschikoff (1912) showed experimentally that tetanus toxin could be extracted from/

from liver cells by means of antitoxin. They allowed the cells to remain in contact with a solution of toxin during one hour at 37° C. Then they removed the cells and washed them free of the surrounding toxin. Some of these washed cells were injected into mice and caused tetanus. The remainder were soaked in a solution of tetanus antitoxin for one hour at 37° C. and then removed from the serum, washed free from the surrounding antitoxin and injected into mice which remained quite well. Control experiments showed that while toxin could pass into the cell and be so firmly fixed that several washings could not remove it, serum, on the other hand, could not pass into the cell in any demonstrable quantity. It is justifiable therefore to presume that the toxin was extracted from the liver cells and that it is advisable to have as high a degree of concentration of antitoxin as possible in the fluid surrounding cells that have been poisoned.

These results suggest the importance of endeavouring to obtain as great a concentration of antitoxin as possible in the central nervous system.

THE ROUTE.

Antitetanic serum may be administered curatively by six different routes. Of these, two, the intracerebral/

intracerebral and intraneural are used comparatively rarely and by general consent are reserved for desperate cases. The remaining four are the intrathecal, the intravenous, the intramuscular and the subcutaneous routes. There are great differences of opinion as to the relative value of these.

In choice of a route one is influenced by physiological considerations, experimental and clinical evidence and statistical data. To attempt to reach a decision by relying on statistical data is particularly hazardous when we have to deal with tetanus. Cases of the disease vary so much in severity. It is also difficult to justify a preference from physiological reasons because we have to begin with a number of assumptions which may or may not be correct. For instance it is maintained by one school that the cerebro-spinal fluid affords us the best channel for bringing the antitoxin into contact with the damaged nerve cells while another school upholds the blood as the best medium. Sufficient clinical evidence to help us to decide is not as yet forthcoming. At the present stage of our experience in the therapeutic use of tetanus antitoxin, experimental evidence seems to promise us most help in determining our choice as to the route of administration.

THE INTRATHECAL ROUTE.

In the Memorandum published by the War Office Committee it is stated that "experimental and clinical evidence has shown that the best results are obtained by intrathecal injections of serum"; and again, "in a case of tetanus the first thing to do is to give an intrathecal injection of antitoxin."

Advocates of this route hold that it affords the most reasonable prospect of getting, in the shortest possible time, fairly large quantities of antitoxin in strong concentration into close relationship with the poisoned cells in the central nervous system. Against it is urged the small size of the dose unless serum containing a relatively large number of antitoxin units per cubic centimetre is used, and that the use of this route depends for its success on two assumptions, namely, that the antitoxin shall actually come into contact with the damaged nerve cells and that, having done so, shall be able to neutralize or dissociate from these cells the toxin that has reached them. Another objection is the danger of contamination and meningitis. It is stated that in specimens of cords removed after death from tetanus definite signs of meningitis having followed the lumbar punctures have/

have been found. This objection becomes of little value, however, when strict antiseptic precautions are taken.

It is also suggested that the limiting membranes of the spinal canal which are so delicately constituted and whose functions are so little understood may be injured by the antiseptics usually added to antitoxin as a preservative. To this Flexner and others have stated that the small amount of preservative is a negligible quantity. Besides that, aqueous solutions of the dried serum may be used if preferred.

Experimental evidence is strongly in favour of the adoption of this route.

Descos and Barthelemy (1902) showed experimentally that this was the best route.

Von Graff (1912), after a number of experiments in the Serotherapeutic Institute in Vienna, concluded that the intrathecal was the most effective route and that next to it came the intravenous.

Permin (1913) showed that when tetanus toxin was injected into the muscles in suitable dose local tetanus was prevented when antitoxin was given intrathecally at the same time, whereas it was not prevented by the same dose of antitoxin given intravenously; not/

not even intrathecal injection prevented tetanus if it was given four hours after the toxin. He used dogs and rabbits in these experiments.

Park and Nicoll injected into the muscles of the hind leg of guinea pigs two minimal lethal doses of toxin, waited till spasms of the leg commenced and then tried antitoxin by various routes. Of 18 guinea pigs 2 controls without antitoxin died in 3 days; 6 received 100 and 200 units of antitoxin by the intracardiac route, and 4 received 200 units intraneurally; all these 10 animals died in from three to eight days. The remaining 6 received intrathecal doses, 3 receiving 10 units only and the other 3 getting 50 units. Of these 6 animals 5 recovered.

Professor C. S. Sherrington, a member of the Tetanus Committee has lately carried out a number of experiments on monkeys. A small cross-cut was made in the outer head of the gastrocnemius muscle, a weighed dose of the dried toxin was inserted, the wound in the muscle and skin being then stitched up.

Of 10 untreated control monkeys all died. Of those treated with antitoxin subcutaneously, all died. Of 12 treated by intramuscular injection, all died. Of 16 treated by intravenous injections 10 died (62.5 per cent mortality). Of 18 treated by intrathecal injections/

injections 5 died (27.7 per cent mortality).

Captain Golla, R.A.M.C., has also lately conducted some experiments at the physiological laboratory of the University of London. The animals used were cats and rabbits, which have a high resistance to tetanus and in which the symptoms develop comparatively slowly.

He used the subcutaneous, intravenous and intrathecal routes. The results of his experiments suggest that the intrathecal route is the best, the intravenous is slightly and the subcutaneous very much inferior to it.

THE INTRAVENOUS ROUTE.

This route is still strongly advocated by some observers. Absorption of the serum after intramuscular and subcutaneous injections is relatively slow. If a large volume of serum, moreover, is injected beneath the skin or into the muscles the resulting swelling is not without pain to the patient. An intravenous injection is the quickest method of rendering the blood rich in antitoxin.

Very large doses have been administered in this way at one time, considerably larger than can be attempted by the intrathecal route.

The/

The advantage claimed for the intrathecal method is that the antitoxin most readily reaches the essential seat of the mischief - the cells of the central nervous system.

The cerebro-spinal fluid is chiefly remarkable in its chemical composition for its low protein content, in which respect it differs markedly from lymph. It is supposed to be secreted by the choroid plexus and is probably absorbed and drained away by the meningeal veins and cranial sinuses. The existence of lymph channels has not been proved or disproved in the central nervous system. Statements have been made that the cerebro-spinal fluid takes the place that the lymph does in other parts of the body. But the function of the lymph in the tissues being that of a kind of "middleman" between the blood and the cells we are therefore asked to believe that the very important cells of the central nervous system depend on a fluid, poor in protein and secreted by a comparatively small gland with a relatively limited blood supply. But all parts of the brain and spinal cord are richly supplied with arteries and capillary vessels which ramify around the cells in the grey matter, and it is probable that the capillaries of the brain perform/

perform the same function as do the capillaries of the rest of the body. It is therefore reasonable to suppose that antitoxin can pass from the capillaries to the cells in the central nervous system as readily as it can do in the tissues of the rest of the body and on this assumption the intravenous route should be just as, if not more, effective than the intrathecal.

While a priori reasoning from physiological considerations may have something to say in favour of the intravenous route as compared with the intrathecal, experimental evidence is all in favour of the latter route. The results of the experimental work of Von Graff, Permin and Sherrington clearly uphold the advantages of the intrathecal route as against the benefits conferred by the intravenous. Golla's work, however, was not conclusive on this point.

The great objection to the intravenous route is the danger of anaphylaxis. Those who have used it extensively, however, claim that the risks are much smaller than would at first appear probable. Very large doses, as much as 30000 units in 120 to 190 cc.s of the serum, have been given at one intravenous injection with no symptoms whatever of anaphylaxis occurring in many instances. In a certain proportion of the cases urticaria has been noticed and has been the/

the only symptom, but this is comparatively common when large doses of the serum are given even by the subcutaneous route. In Case II a transient urticarial rash appeared on the shoulders and chest of the patient, the result of subcutaneous injections. Administration of serum was discontinued for a day and the rash never reappeared. Some of the cases showed oedema of the eyelids as well as the urticaria. In only one case of those on record have I been able to find evidence of definite anaphylactic shock with feeble pulse and weakened action of the heart. One death occurred under the anaesthetic while an intravenous injection was being given, but there was no reason for ascribing it to anaphylaxis. On the other hand there was one death after an intrathecal injection and in this instance it was attributed to anaphylaxis.

THE INTRAMUSCULAR AND THE SUBCUTANEOUS ROUTES.

These two routes may appropriately be considered together as they are essentially similar in their action, each being a comparatively slow and continuous method of dosage when compared with the rapid method aimed at by the intrathecal and intravenous routes. Hitherto they have been mainly considered as supplementary to the other routes and have been used to introduce the serum at intervals with the object of keeping/

keeping up the concentration of antitoxin in the tissues and system after the critical stage has been tided over, and of preventing a recurrence of acute symptoms. But Leishman and Smallman, reasoning from analysis of the results obtained in their last published series of cases, are inclined to raise these routes to a more dignified position. They believe that their records show that when the dosage has been sufficient and when these two paths of introduction have been utilized freely their results have been more satisfactory than when they were not utilized or were employed in too restricted a fashion.

From theoretical considerations there is something to be said in favour of their view. In a case of tetanus we have to deal with the local factory of the toxin, the line of transit to the central nervous system and the central nervous system itself. Dealing with the local factory or the wound has proved to be inadvisable. It ends often in failure or in a sudden outpouring and absorption of the toxin. To make an attempt on the central nervous system is to attack a stronghold where the enemy has established himself and which he holds in great strength. That is the plan adopted when we employ the intrathecal route. It is based on the assumption that dissociation of toxin/

toxin from the poisoned nerve cell is realizable in practice. On this point there is considerable divergence of opinion. The good effect of intrathecal injections of serum in some cases of cerebro-spinal meningitis has no real bearing upon this problem because, in that instance, we are attacking an organism known to be present in the cerebro-spinal fluid.

There remains the third alternative the attack on the lines of communication. Success by this plan would appear more hopeful if the attack could be sustained steadily, continuously and in sufficient concentration of force on the path or paths which the toxin must follow in travelling to the brain. When we introduce the antitoxin intravenously, even in large doses, it is rapidly diluted by the whole volume of the blood in the body and ultimately by the lymph as well, and it is improbable that it will be present in sufficient concentration where it is most needed. When the injections are intramuscular or subcutaneous the dilution is by no means so rapid. It is stated that serum takes 48 hours to become diffused when introduced subcutaneously and 24 hours when an intramuscular injection is given. This slow rate of absorption may in reality be a virtue instead of a disadvantage, especially if the inoculations are made in/

in the neighbourhood of the nerves that are suspected of transmitting the toxin. We can in this way produce a zone of tissue bathed in antitoxin in far greater concentration than can be produced in the blood and lymph of the part by means of intravenous injections. If this reasoning is sound, the best method, in the case of a single wound and particularly if it be situated on a limb, would be to introduce the antitoxin both subcutaneously and intramuscularly on each surface of the limb and at different depths amid the muscles or, in other words, astride the path of transmission of the toxin on its way to the spinal cord.

Experimental evidence, it must be admitted, is distinctly against the employment of these routes to the exclusion of the intravenous and intrathecal.

THE BEARING OF STATISTICAL DATA ON THE QUESTION OF ROUTE.

Since the beginning of this war five analyses of cases of tetanus have been communicated, three by Sir David Bruce with reference to cases in the home hospitals, and two by Sir William Leishman of cases which occurred in France.

In all, reports on 965 cases have been dealt with;
of/

of these 405 recovered and 560 died - a mortality of 58.0 per cent. The first series was communicated by Sir William Leishman (July 1915), 179 cases of which 140 died, a case mortality of 78.2 per cent. Then followed in order successive reports by Bruce (October 1915), 231 cases with 98 recoveries and 133 deaths - a case mortality of 57.7 per cent; Bruce (December 1916) 195 cases, 99 recoveries, 96 deaths - mortality 49.2 per cent; Leishman and Smallman (March 1917), 160 cases, 42 recoveries, 118 deaths - mortality 73.7 per cent; and lastly by Bruce (June 1917), 200 cases with 127 recoveries and 73 deaths - a mortality of 36.5 per cent.

Leishman and Smallman in their second series have gone into an elaborate analysis of their results with special reference to the route of administration. I have drawn up a table, based on one of theirs, but have included all the cases in the reports of the home hospitals in which details are given of the methods of administration of the antitoxin. Unfortunately for my purpose, in many of these cases where a combination of the different routes has been used, the necessary details are not forthcoming.

Of the four routes under consideration there are no fewer than fifteen possible combinations. In the/

the table an initial letter is used to signify the particular route, thus "T" = the intrathecal method, "V" = the intravenous, "S" = the subcutaneous and "M" = the intramuscular. In each group is shown the number of cases, the number of deaths and the case mortality.

Table/

Table showing Number of Cases treated by Serum together with the Number of Deaths and the Case Mortality per Centum. The Table also shows the Number of Cases treated by any one of the Four Available Routes alone or in Combination with one or more of the other Three Routes.

Method of Administration.	Number of Cases	Number of Deaths	Case Mortality.
T	63	39	61.9 per cent.
V	26	18	69.2 " "
S	242	130	78.5 " "
M	25	5	20.0 " "
TV	16	12	75.0 " "
TS	69	39	56.5 " "
TM	13	9	69.2 " "
VS	21	16	76.2 " "
VM	2	0	0 " "
SM	1	1	100.0 " "
TVS	36	25	69.4 " "
TSM	4	1	25.0 " "
TVM	5	3	60.0 " "
VSM	1	1	100.0 " "
TVSM	2	1	50.0 " "
Totals	526	300	57.0 " "

In/

In his first communication Leishman gave no details of the method of administration and none of the cases of that series are included in this table. In the four remaining reports details were given in every case where only one of the four routes were used and for that reason the figures given with reference to groups "T", "V", "S" and "M" form a fair basis for comparison. They would appear to suggest that the subcutaneous route when used alone is the least successful and that the intramuscular is the most favourable one.

The groups are very uneven in size and it would be futile to attempt to form any conclusions from a consideration of the degree to which the case-mortalities are above or below the mean rate of the total number of cases.

The intrathecal and intravenous routes do not appear to promise any great measure of success.

The whole question has to be left very much where it was and it does not seem legitimate to draw any very definite conclusions from the data at present available.

THE/

THE INFLUENCE OF DOSAGE ON CURATIVE ACTION.

Tetanus antitoxin being an antitoxic rather than a bactericidal serum, it is reasonable to expect that the exhibition of large doses would prove more successful than its use in small quantities. It is generally held that, if antitetanic serum is to be used curatively, it must be used in big doses. Details of the dosage have been given by Bruce and Leishman in their reports:

The Total Quantity of Antitoxin given during the attack.

Out of 730 cases -

19 received 1000 units or under, 13 died.

180 " 1001 to 5000 units, 16 "

127 " 5001 " 10000 " , 77 "

156 " 10001" 20000 " , 90 "

230 " 20001" 100000 " , 84 "

18 " above 100000 " , 4 "

If we divide these cases into those which received less or more than 20000 units we have 482 cases which received the smaller quantity, with 294 deaths, a case mortality of 61 per cent; while 248 cases received more than 20000 units, with 88 deaths, a case mortality of 35.5 per cent. This difference of 25.5 per cent is a marked one, but it would be false to/

to argue that the cases in the latter category showed a better recovery rate because of the larger quantity of serum given. A serious case resulting in death after 2 or 3 days naturally would not be given as large a total quantity of antitoxin as a milder case where the dose would be repeated day after day.

NON-SPECIFIC TREATMENT.

(1) Carbolic acid injections.

This method of treatment was first described by Bacelli in 1888. In 190 collected cases he showed a gross mortality of 17.4 per cent. It was also reported on very favourably by several Italian writers, but experimental evidence has proved it to be valueless.

It consists in the subcutaneous or intramuscular injection of a 2 to 5 per cent solution of carbolic acid, 3 to 12 grs. of the acid being a daily dose. The injections may be given 2 hourly or 4 hourly.

The cases have to be carefully watched for signs of carboluria and it is deemed advisable to discontinue the injections temporarily if pigmentation or albuminuria manifest themselves. To obviate this tendency by encouraging diuresis Bacelli recommended the administration of daily doses of 20 grs. of sodium sulphate.

In the analyses of Bruce and Leishman this method of/

of treatment is recorded as having been adopted with or without specific treatment in 57 cases. Of these 37 died - a case mortality of 64.9 per cent.

It is being used less and less and few retain any faith in it.

(2) Magnesium Sulphate.

The treatment of tetanus by injections of magnesium sulphate is based on the investigations of Meltzer and Auer who found that magnesium sulphate and magnesium chloride when injected into animals subcutaneously in proportion of 1.5 grm. to 1 kilo. of body weight, produce deep sleep with muscular relaxation and abolition of all the reflexes except the conjunctival.

Falk (1914) reported some severe cases of tetanus treated very successfully by subcutaneous injections of magnesium sulphate. Three injections were given every 24 hours and continued for a fortnight. The amount given varied according to the severity of the symptoms from 0.45 to 4 grms. The larger doses were dangerous, alarming symptoms (including apnoea for 20 minutes in one case) being observed when the drug had been given for 10 days. There seems to be a cumulative effect.

Pellaval, Kocher's assistant, first used magnesium sulphate/

sulphate by the intrathecal route on 5 severe cases of tetanus in the Turco-Bulgarian War. Of these 2 recovered.

With reference to the method of administration some prefer giving 2 ccm. of a 25 per cent solution, others prefer giving about 5 to 10 ccm. of a 10 per cent solution. It is always better to give it under an anaesthetic and it must be remembered that the risks are great. Convulsions or cessation of breathing may occur with extreme cyanosis and in some cases acute mania may develop.

Bruce and Leishman state that magnesium sulphate was used intrathecally or subcutaneously in 32 cases. Of this number 24 died - mortality 75 per cent.

Treatment by this method appears to have no effect on the disease itself. The cessation of spasm is only temporary and the risks are great. It is doubtful if any advantage is gained by its use.

(3) Sedative drugs.

Chloral and bromide still remain the most popular remedies for the relief of the spasm. After these morphia probably comes next in favour.

Chloretone has also been greatly used. Its use was popularized in America by the writings of Hutchings/

Hutchings of Detroit. It is given per rectum in doses of 30 to 40 grs. dissolved in olive oil and improvement in the muscular symptoms generally follows in one or two hours. The dose is repeated when its effect passes off, as much as 80 grs. having been given in a day. It is claimed for chloretone that it is the best and least poisonous drug for the relief of tetanic spasm. Other drugs have been used, atropine, omnopon, scopolamine, alcohol, chloroform, ether and paraldehyde with more or less success.

CONCLUSIONS.

- (1) The experience of our own Army as well as that of the French and German establishes beyond doubt the value of prophylactic injections of anti-tetanic serum.
- (2) There is no evidence that 500 units is not a sufficient prophylactic dose in all cases; but in severe wounds and in compound fractures it is better to give a larger dose, 750 to 1000 units at least.
- (3) Experimental evidence and the experience of our hospitals goes to prove that the earlier the administration of the prophylactic dose, the fuller is the measure of protection conferred. Where the initial prophylactic dose is delayed the size of that dose should be increased.
- (4) The protective injections should be repeated every seven days or so as long as there is any sepsis present; and before any operation, however slight, at the site of an old wound, a prophylactic dose of serum should be given.
- (5) The average length of the incubation period has increased, probably as the result of prophylactic injections of antitetanic serum, and the conviction based on former experience that the cases with/

with a short incubation period show as a rule a higher case mortality has been confirmed.

The shortest incubation period recorded is 2 days, the longest 365 days.

- (6) A number of cases of delayed tetanus have occurred and have lent support to the view that tetanus spores may remain undestroyed in the tissues at the site of an old healed wound and may after a period of weeks or months be in some way stimulated to germination and give rise to a severe and perhaps fatal attack of the disease.
- (7) By preventive injections of serum the picture of the onset of symptoms has in a large proportion of the cases been radically altered. Not only has the incubation period been prolonged, but the rate of development of the symptoms has been much slower. In many instances the symptoms have been localised to the muscles in the neighbourhood of the wound and generalized spasms have not occurred.
- (8) A list of premonitory symptoms has been compiled. Experience goes to prove the importance of paying particular attention to the condition of the muscles near the wound. The earliest symptoms manifest themselves there, in the form of twitchings and increased reflex irritability, in/

in some cases for days before there are any signs of the disease becoming generalized. The probability of establishing an earlier diagnosis is increased and treatment can be begun sooner with a better chance for the patient.

- (9) The symptoms of some abnormal forms of tetanus are described.
- (10) Generally speaking, from a study of the cases of tetanus that have been recorded, there is little evidence that the therapeutic use of antitetanic serum has had any effect on the course of the disease.
- (11) In the cases in which the dosage has been large the results on the whole have been more promising than when smaller quantities were used.
- (12) With regard to the route of administration experimental evidence would seem to favour the intrathecal and the intravenous routes in the order named; the intramuscular and subcutaneous routes have not proved of much value when compared with the above.

From the theoretical point of view there is something to be said for each of these routes.

An analysis of the figures recorded in the communications/

communications of Bruce and Leishman, however, gives us no guidance in determining our choice of route. There are slight indications that the intramuscular route may be used with advantage if the injections are given in fairly large quantities at different depths in the tissues and in the neighbourhood of the nerves which are suspected of carrying the toxin from the wound to the cells of the spinal cord. But the general opinion, based apparently on theoretical grounds and experimental evidence, appears to be that it should only be used with the intrathecal or intravenous routes and not employed to the exclusion of these channels of introduction.

- (13) Treatment by carbolic acid injections was adopted in 57 cases. It was not proved of any value.
- (14) Magnesium sulphate in solution was injected intrathecally or subcutaneously in 32 cases. This method has been reported on unfavourably as being risky and affording only temporary cessation of spasm with no effect on the disease itself.
- (15) Of sedative drugs chloral and bromide are the most popular. Morphia has also proved of great value. Chloretone has been used in many cases with good results.

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